BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classificati n [5] :		(11) International Publication Number: WO 91/12008
A61K 31/71, 9/08, 47/32	A1	(43) International Publication Date: 22 August 1991 (22.08.91)

(21) International Application Number: PCT/HU91/00006

(22) International Filing Date: 8 February 1991 (08.02.91)

(30) Priority data:
808/90 15 February 1990 (15.02.90) HU

(71) Applicant *(for all designated States except US)*: CHINOIN GYÓGYSZER ÉS VEGYÉSZETI TERMÉKEK GYÁRA RT.[HU/HU]; Tó utca 1-5, H-Budapest IV (HU).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : Z.SZABÓ, Anna [HU/HU]; Farkashida 17, H-1163 Budapest (HU).

(74) Agent: CHINOIN RT.; Division for Industrial Rights, Tó utca 1-5, H-1045 Budapest (HU).

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, PL, SE (European patent), SU, US.

Published
With international search report.

(54) Title: EYE-DROP

(57) Abstract

The invention relates to an eye-drop, characterized by, that it contains, 0,02 - 0,1 mass % of primycin, 15,0 - 25,0 mass % f pyrrolidon-2, 12,0 - 25,0 mass % of polyoxyethylene-660-hydroxystearate, 1,0 - 5,0 mass % of polyvinyl-pyrrolidon and distilled water to complete to 100 mass percent.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

EYE-DROP

The invention relates to a stable aqueous solution containing as active ingredient primycin and to a process for the preparation thereof.

Subjects of the present invention are further therapeutical compositions prepared from the stable aqueous solution.

Primycin is a macrolide antibiotic agent, which is characterized in the literature (J. Chem. Soc. Perkin I. 1974, p. 816) by a single formula:
/5-(18-(α-D-arabinofuranosyloxy)-2-butyl-3,7,11,15,19,21, 23,25,27-nonahydroxy-4,16,32,34-tetramethyl-1-oxo-oxacyclohexatriakonta-16,32-diene-35-yl-)/4-hydroxyhexyl/guanidium--sulphate.
Although the above literature describes its structure by a single formula, it is known, that it is an antibiotic-mixture consisting of several components (Hungarian Applications No. 2125/84 and 2869/84).

Primycin is a natural antibiotic agent originating from the fungal strain culture Thermopolyspora galeriensis, its preparation via fermentation is described in the Hungarian Patent Specification No. 153.593. Primycin is an antibiotic agent of a large spectrum, and it is firstly effective against gram positive bacteria and against polyresistent humanpathogenic strains too.

Primycin can be effectively applied for the treatment of epithelium lesions, in the urology, surgery, gynecology, dermatology, in the case of household lesions and for the treatment of burns respectively.

In the course of its application neither resistance nor, allergic reactions were experienced.

There are known further combinations of primycin with other antibiotics (Hungarian Patent Specification No. 158.241).

Although primycin is a very effective antibiotic, its therapeutical utilization was made extraordinarily difficult since it is practically insoluble in water.
Thus, several efforts had earlier been made to eliminate these difficulties and to prepare pharmaceutical compositions containing primycin in a therapeutically well utilizable form while maintaining its efficiency as a whole.

The Hungarian Patent Specification No. 173.708 publishes heterocolloidal therapeutical compositions containing primycin. Their disadvantage is the low primycin content (0.2-1.0 %). Further the ethyl alcohol used for the preparation of the heterocolloidal solution has in some cases skin irritating effect and in the case the alcohol is vaporized from the treated surface one part of the primycin is running down from the skin without exerting a biological effect. This formulation cannot be used to prepare eye-drops.

The Hungarian Patent Specification No. 194.493 describes a basic gel containing primycin and N-methyl-pyrrolidon from which therapeutical compositions and different gels were prepared. This composition having a gel consistency is useful to incorporate the active ingredient practically in all qalenic forms such as ointments, creams, foams and the like, however it is not useful to prepare eye-drops.

The aim of our invention was to prepare a stable aqueous solution containing primycin as active ingredient, which is free from alcohol and does not contain eye-irritating substances and this way it is suitable for the preparation of eye-drops.

According to the facts set forth ab ove the invention relates to eye-drops characterized by, that they contain
0,02 - 0,1 mass % of primycin,
15,0 - 25,0 mass % of pyrrolidon,
12,0 - 25,0 mass % of polyoxyethylene-660-hydroxystearate,
1,0 - 5,0 mass % of polyvinyl-pyrrolidon and
distilled water needed to complete to 100 mass %.

The eye-drops according to the invention are prepared in a way, that primycin is dissolved by heating in pyrrolidon-2 (Soluphor P) and to the warm solution the polyoxyethylene--660-hydroxystearate (Solutol HS 15) and polyvinyl-pyrrolidon are added. The distilled water is added to the system while stirring quickly and the solution is cooled to room-temperature while stirring.

The eye-drops according to our invention cause no eye-irritation by a 14 days treatment as it has been proved by animal experiments carried out on New Zealand rabbits.

The eye-drops according to the invention may contain beside the primycin known antimicrobic active ingredients as norfloxacin, pefloxacin, cyprofloxacin, ofloxacin too.

The compositions according to the invention are illustrated by the following non limiting Example.

EXAMPLE

An eye-drop with the following composition is prepared

Primycin	0,05	mass %
Soluphor P	20,0	mass %
Soluptol HS	15,0	mass %
Polyvinyl-pyrrolidon	3,0	mass %
Distilled water ad.	100,0	mass %

What we claim is:

1. Eye-drop, characterized by, that it contains
   0,02 - 0,1 mass % of primycin
   15,0 - 25,0 mass % of pyrrolidon-2
   12,0 - 25,0 mass % of polyoxyethylene-660-hydroxy-stearate
   1,0 - 5,0 mass % of polyvinyl-pyrrolidon
   and distilled water to complete to 100 mass percents.

2. Eye-drop according to claim 1, characterized by, that it contains
   0,05 mass % of primycin
   20,0 mass % of pyrrolidon-2
   15,0 mass % of polyoxyethylene-660-hydroxystearate
   3,0 mass % of polyvinyl-pyrrolidon
   and distilled water to complete to 100 mass percents.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 91/00006

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.[5]: A 61 K 31/71, 9/08, 47/32

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl.[5]	A 61 K 31/00, 9/00, 47/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

AT

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	WO, A1, 85/05 621 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 19 December 1985 (19.12.85), see claims 50,57,60; example 37.	(1,2)
A	AT, B, 344 885 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 15 December 1977 (15.12.77), see claim 1; examples 7,13.	(1,2)
A	GB, A, 1 512 604 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 01 June 1978 (01.06.78), see claims 1,5; examples 11,12.	(1,2)
A	EP, A2, 0 224 868 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 10 June 1987 (10.06.87), see abstract; claims 1,11.	(1,2)
A	DE, A1, 3 104 282 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 28 October 1982 (28.10.82), see example 6.	(1,2)
A	CH, A, 543 278 (BURTON PARSONS CHEMICALS, INC.) 14 December 1973 (14.12.73), see claims 1,10-12; column 8, lines 22-54.	(1,2)

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03 April 1991 (03.04.91)	12 April 1991 (12.04.91)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (C NTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	GB, A, 1 340 518 (BURTON PARSONS CHEMICALS, INC.) 12 December 1973 (12.12.73), see example 1; page 4, lines 11-16, 69-105.	(1,2)
A	DE, A, 2 615 140 (NELSON RESEARCH & DEVELOPMENT CO.) 21 October 1976 (21.10.76), see claims 1-3, 17-19; page 3, lines 13-20.	(1,2)

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 91/00006 .

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La prés nte annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO-A1- 8505621	19-12-85	CA-A1- 1274508	25-09-90
		DK-A - 460/86	30-01-86
		DK-A0- 460/86	30-01-86
		EP-A1- 182851	04-06-86
		FI-A - 860426	29-01-86
		FI-A0- 860426	29-01-86
		FI-B - 80046	29-12-89
		FI-C - 80046	10-04-90
		HU-A2- 39187	28-08-86
		HU-B - 196425	28-11-88
		IL-A0- 75357	29-09-85
		JP-T2-61502398	23-10-86
		US-A - 4873348	10-10-89
		HU-A2- 39186	28-08-86
		HU-B - 195514	30-05-88
		CN-A -85104165	26-11-86
		CN-A - 1043627	11-07-90
		CN-B - 1009082	08-08-90
AT-B - 344885	10-08-78	AT-A - 4392/76	15-12-77
		BE-A1- 843115	18-10-76
		ES-A5- 449062	15-11-77
		ES-A1- 449062	16-11-77
		FI-A - 761772	21-12-76
		FI-B - 55609	31-05-79
		FI-C - 55609	10-09-79
		FR-A1- 2315910	28-01-77
		FR-B1- 2315910	15-12-78
		GB-A - 1512604	01-06-78
		GR-A - 60551	14-06-78
		HU- P- 173708	28-07-79

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
		JP-A2-52007419	20-01-77
		JP-B4-62022968	20-05-87
		SU-A3- 1338778	15-09-87
GB-A - 1512604	01-06-78	AT-A - 4392/76	15-12-77
		AT-B - 344885	10-08-78
		BE-A1- 843115	18-10-76
		ES-A5- 449062	15-11-77
		ES-A1- 449062	16-11-77
		FI-A - 761772	21-12-76
		FI-B - 55609	31-05-79
		FI-C - 55609	10-09-79
		FR-A1- 2315910	28-01-77
		FR-B1- 2315910	15-12-78
		GR-A - 60551	14-06-78
		HU- P- 173708	28-07-79
		JP-A2-52007419	20-01-77
		JP-B4-62022968	20-05-87
		SU-A3- 1338778	15-09-87
EP-A2- 224868	10-06-87	CN-A -87100114	25-05-88
		DK-A0- 5684/86	26-11-86
		DK-A - 5684/86	28-05-87
		EP-A2- 224868	10-06-87
		EP-A3- 224868	26-08-87
		FI-A0- 864795	25-11-86
		FI-A - 864795	28-05-87
		HU-B - 197989	28-07-89
		JP-A2-62181217	08-08-87
		KR-B1- 8903842	05-10-89
		NO-A0- 864718	25-11-86
		PL-A1- 262631	21-07-88
		YU-A - 2027/86	30-06-88
		YU-A - 2286/87	31-08-88
		DD-A5- 258745	03-08-88
		DK-A0- 5684/86	26-11-86
		DK-A - 5684/86	28-05-87
		EP-A3- 224868	26-08-87
		FI-A0- 864795	25-11-86
		FI-A - 864795	28-05-87
		HU-A2- 42320	28-07-87
		HU-B - 194493	29-02-88
		JP-A2-62181217	08-08-87
		NO-A0- 864718	25-11-86
		PL-B1- 151121	31-08-90
		YU-A - 2027/86	30-06-88
		YU-A - 2286/87	31-08-88
DE-A1- 3104282	28-10-82	DE-C2- 3104282	26-07-90

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International S arch Report on International Pat nt Application No. PCT/HU 91/00006

Annexe au rapport de recherche internationale relatif à la demand de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
CH-A - 543278	14-12-73	US-A - 3767788	23-10-73
		CA-A1- 970687	08-07-75
		DE-A - 2051369	09-06-71
		DE-B2- 2051369	04-10-79
		DE-C3- 2051369	19-06-80
		GB-A - 1340515	12-12-73
		GB-A - 1340517	12-12-73
		JP-B4-54021405	30-07-79
		NL-A - 7015332	03-06-71
		US-A - 3755561	28-08-73
		US-A - 3767789	23-10-73
		US-A - 3856919	24-12-74
		US-A - 3947573	30-03-76
		FR-A5- 2073437	01-10-71
		FR-B1- 2073437	01-08-75
GB-A - 1340518	12-12-73	GB-A - 1340516	12-12-73
DE-A - 2615140		DE-A1- 2615140	21-10-76
		DE-C2- 2615140	27-11-86
		FR-A1- 2313080	31-12-76
		FR-B1- 2313080	05-10-79
		GB-A - 1538903	24-01-79
		JP-A2-51128419	09-11-76
		JP-B4-58022010	06-05-83
		US-A - 4039664	02-08-77